IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Pastan et al.
Application No. 10/537,061
Filed: June 1, 2005
Confirmation No. 2145
For: RECOMBINANT IMMUNOTOXIN AND USE IN TREATING TUMORS
Examiner: David J. Blanchard
Art Unit: 1653
Attorney Reference No. 4239-67287-05

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SECOND DECLARATION OF DR. PASTAN UNDER 37 CFR § 1.132

1. I, Ira Pastan, M.D., am an inventor of the above-referenced application.

2. It is my understanding that claims 1-4, 6-8, 10-13 and 21-23 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Modak et al. (Cancer Res. 61: 4048-4054, 2001) in view of U.S. Patent No. 5,618,920 (Robinson et al.) and Reiter et al. (Biochemistry 33: 5451-5459, 1994) and U.S. Patent No. 5,530,101 (Queen et al.). Claims 1-3, 6-8, 10-12 and 21-23 were rejected under 35 U.S.C. § 103 (a) as allegedly being obvious over U.S. Published Patent Application No. 2002/102264 (Cheung[a]), in view of Robinson et al., Queen et al. and Reiter et al. Claims 1-3, 6-8, 10-12 and 21-23 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Published Patent Application No. 2003/0103933 (Cheung [b]) in view of Robinson, Reiter et al. and Queen et al. Claims 1-3, 6-8, 10-12 and 21-23 are rejected under 35 U.S.C. § 103 (a) as allegedly being obvious over U.S. Published Patent Application No. 2005/0169932 A1 (Cheung[c]) in view of Robinson et al., Reiter et al., and Queen et al.

3. The final Office action dated August 14, 2007 acknowledges that the dsFv form of 8H9 provides superior results compared to the scFv form of 8H9. However, the final Office

action alleges that the findings presented in my Declaration submitted on May 18, 2007 would have been predicted, as "the evidence submitted does not prove any results beyond what one of ordinary skill in the art might have expected adequate to rebut the *prima facie* case of obviousness" (page 8 of the final Office action). It is my understanding that the Office action requests evidence that would document that the previous experimental results presented in my Declaration of May 18th, such as the monkey cytotoxicity, would not have been predicted by one of skill in the art.

4. As described in my Declaration of May 18th, 8H9(dsFv)-PE38 was not toxic in Cynomolgus monkeys.[1] Specifically, one monkey received 0.1 mg/kg (100 μg/kg) daily for three days and the second received 0.2 mg/kg (200 μg/kg) daily for three days. In this study, both monkeys tolerated 8H9(dsFv)-PE38 well with only mild laboratory abnormalities. Serum levels of 8H9(dsFv)-PE38 were determined in each of the two monkeys ten minutes after each of the three doses. The injection of 0.1 mg/kg of 8H9 dsFv-PE38 did not produce any increase in the level of liver enzymes in the blood of these monkeys and the injection of twice the dose produced only a small increase in liver enzymes. Thus, 8H9(dsFv)-PE38 was not toxic in a primate model.

5. This is in stark contrast to the results obtained with another dsFv-PE38 antibody, namely SS1P(dsFv)-PE38, which binds mesothelin (another antigen expressed in cancer). A toxicology study of intravenous SS1(dsFv)-PE38 was performed. Groups of four animals (two males and two females per group) were treated at 75 μg/kg, 0.3 mg/kg (300 μg/kg) and 1,000 μg/kg (1 mg/kg) intravenously daily for five days, and at 0.1 mg/kg (100 μg/kg) intravenously daily for ten consecutive days; two control animals (1 male + 1 female) were treated with vehicle only. Dermatologic injury was documented in all treatment groups, with erythema, exudation and breakdown with scab formation. Although predominantly involving the injected hind limb, dermal injury was occasionally evident on face or forelimb. A dose-dependent decline of serum albumin and phosphate was noted in all treatment groups. Upon autopsy, dose-related

[1] There is a similar reactivity of monkey and human tissues with 8H9 (Modak et al., *Cancer Res.* 61:4048-4054, 2001). These studies were not performed with the scFv form.

inflammatory reactions of serosal membranes were documented microscopically in all treated monkeys, involving pleura, pericardium and capsules of liver and spleen.

In the animals treated with 300 μg/kg and 1,000 μg/kg additional effects were observed, such as poor appetite and decreased activity. Tremor and ataxia were noted in high-dose animals, persisting after treatment. Elevation of liver enzymes (AST, ALT and LDH) was observed at both 300 and 1,000 μg/kg; a mild decrease in renal function was found at 1,000 μg/kg; a mild elevation of alkaline phosphatase (AlkPhos) and bilirubin was also found at 1,000 μg/kg. Marked decrease of serum iron and moderate neutrophilic leukocytosis were probably due to an inflammatory reaction. One death (25%) occurred in the group receiving 300 μg/kg and the group receiving 1,000 μg/kg. Adhesions of diaphragmatic lobes of lung to diaphragm were evident grossly in the highest dose group. Inflammation of the serosal surface of the stomach was also noted in several animals. Severe epicarditis, particularly in the atrial regions, was observed in several animals at higher doses, and could have been responsible for the deaths. Thus, SS1P(dsFv)-PE38 was toxic at all doses, as it caused dermatologic injury and inflammatory reactions. Severe toxicity was noted at 300 μg/kg and 1,000 μg/kg.

7. In view of the data on other dsFv-PE38 antibodies, such as SSIP(dsFv)-PE38, one of skill in the art would predict that a dsFv-PE38 antibody would be toxic. The lack of toxicity of 8H9(dsFv)-PE38 was unexpected and could not be predicted.

8. One of skill in the art would predict that the dsFv form and the scFV form of an antibody would be similarly toxic, or that the dsFv form would be more toxic (if the dsFv form was more stable than the scFv form). To test the toxicity of SS1P(scFv)-PE38, cynomolgus monkeys were treated with three daily doses of 50 and 500 μg/kg. Decreased appetite and physical activity were noted in animals at 500μg/kg; a transient elevation of liver enzymes was also observed. Thus, the SSIP(scFv)-PE38 was toxic in monkeys at similar doses to SSIP(dsFv)-PE38.

As presented in my Declaration of May 18th, the LD_{50} of 8H9(scFv)-PE38 was less than 0.2 mg/ml, while the LD_{50} of 8H9(dsFv)-PE38 was 1.0 to 0.75 mg/ml. The fact that the toxicity of 8H9(dsFv)-PE38 was substantially less than the toxicity of 8H9(scFv)-PE38 (while the

stability of the 8H9(scFv)-PE38 was greater) was unexpected. The unexpected nature of the results is supported by the data obtained for SSIP(dsFV)-PE38 and SSIP(scFV)-PE38.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of the Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Ira Pastan, M.D.

10/24/07
Date